

***Amendments to the Drawings***

Attached are 4 sheets of Replacement Drawings for Fig. 4, Figs. 5-6, Figs. 7-8, and Fig. 9. Please replace the originally filed sheets corresponding to Fig. 4, Figs. 5-6, Figs. 7-8, and Fig. 9 with the drawings attached hereto.

Attachments: 4 sheets of Replacement Drawings, 4 sheets of Annotated Drawings.

***Remarks***

Upon entry of the foregoing amendment, claims 1-37, and 39-41 are pending in the application, with claims 1, 39 and 40 being the independent claims. Claims 31-37 and 39-41 are withdrawn from consideration. Claims 1 and 18 are sought to be amended. The amendments to the claims place them in better form for consideration. These changes are believed to introduce no new matter, and their entry is respectfully requested.

***Sequence Compliance***

The Examiner contends that the application does not comply with the requirements of 37 C.F.R. 1.821-1.825 and states "for the reason(s) set forth below," however no reasons are given by the Examiner. Applicants respectfully request that the Examiner provide clarification regarding compliance with the sequence rules in the next action.

The specification has been amended to direct the entry of the attached Substitute Sequence Listing at the end of the application. The specification recites amino acid and nucleic acid sequences that require a sequence listing identifier and were inadvertently omitted from the original sequence listing. Accordingly, the Substitute Sequence Listing has been amended to include SEQ ID NOs: 176-207.

In accordance with 37 C.F.R. § 1.825(a), this submission includes no new matter.

In accordance with 37 C.F.R. § 1.825(b), the paper copy of the Substitute Sequence Listing and the computer readable copy of the Substitute Sequence Listing

submitted herewith are the same. Applicants respectfully request that the attached Substitute Sequence Listing be entered.

***Objections to the Specification***

The Examiner noted that the specification has not been checked for minor errors and requested Applicants' cooperation in correcting any errors. Applicants have reviewed the specification and have amended the specification accordingly.

Applicants have amended the specification to capitalize trademark terms and include generic terminology.

Applicants have amended the specification to include the appropriate sequence identifiers that were inadvertently omitted from the original specification.

Applicants have amended Fig. 4, Figs. 5-6, Figs. 7-8, and Fig. 9 to include the appropriate sequence identifiers that were inadvertently omitted from the originally submitted figures. Pursuant to 37 C.F.R. § 1.84(c), Applicants submit herewith 4 sheets of Replacement Drawings of Fig. 4, Figs. 5-6, Figs. 7-8, and Fig. 9. 4 sheets of Annotated Drawings of Fig. 4, Figs. 5-6, Figs. 7-8, and Fig. 9, indicating changes made, are submitted herewith.

No new matter has been added by way of these amendments.

***Rejections under 35 U.S.C. 101***

The Examiner rejected claims 1-30 under 35 U.S.C. § 101 because the claims are allegedly directed to non-statutory subject matter. The Examiner contends that the claims are directed to products of nature, and as such, are not patentable, because they do not reflect the "hand of man." The Examiner suggests recitation of "isolated polypeptide," for example. Applicants respectfully traverse this rejection.

Applicants respectfully disagree with the Examiner. Applicants respectfully point out that in contrast to clostridial neurotoxin holotoxin, the presently claimed single-chain polypeptides are *incapable* of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds. In addition, the presently claimed single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated H<sub>C</sub>. Furthermore, the specific SEQ ID NOs recited in claim 1 include one or more features that are not present in "native" clostridial neurotoxins, such as, at least one of a non-native protease activation site, spacer/linker peptide, C-terminal peptide ligand/tag, N-terminal extension and/or amino acid variation(s).

Hence, the claimed invention reflects "the hand of man" and is not directed towards non-statutory subject matter. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

***Rejections under 35 U.S.C. 102***

The Examiner rejected claims 1-30 under 35 U.S.C. § 102(b), as allegedly anticipated by Binz *et al.*, *Eur. J. Biochem.*, 189:73-78 (1990). The Examiner alleges that

Binz *et al.* teach a fragment of SEQ ID NO:66 which anticipates the claims. The Examiner alleges that the Binz *et al.* polypeptide fragment is capable of cleaving vesicle/plasma membrane associated proteins essential to exocytosis. Applicants respectfully traverse this rejection.

Applicants respectfully assert that the claims are novel over Binz *et al.* The sequence recited in Binz *et al.* is full length BoNT/A holotoxin, and therefore comprises a functional C-terminal part of a clostridial neurotoxin heavy chain designated H<sub>C</sub>. In contrast, the pending claims explicitly recite the *absence* of a functional C-terminal part of a clostridial neurotoxin heavy chain designated H<sub>C</sub>. Accordingly, the single-chain polypeptide of the present invention *lacks* the ability to bind to cell surface receptors that are the natural cell surface receptors to which the native clostridial neurotoxin binds.

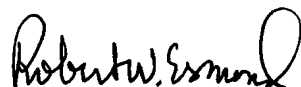
Accordingly, Applicants respectfully submit that the pending claims are novel over Binz *et al.*, and Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

***Conclusion***

Prompt and favorable consideration of this Amendment and Reply is respectfully requested. Applicants believe the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

A handwritten signature in black ink, appearing to read "Robert W. Esmond". The signature is fluid and cursive, with a large loop at the end.

Robert W. Esmond  
Agent for Applicants  
Registration No. 32,893

Date: October 6, 2008

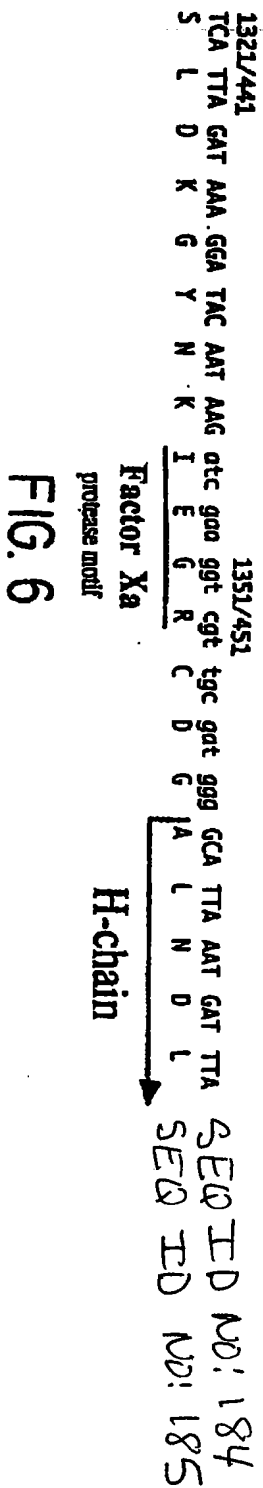
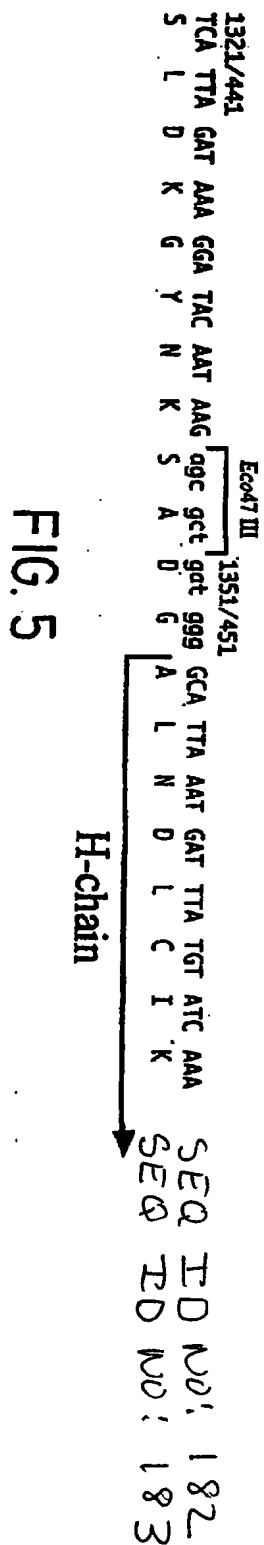
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MPFV NKQFN YKDPVNGVDIA YIKIPN AGQM QPV  
SEQ ID NO: 181

FIG. 4

FIG. 4





IGF-1

2587/863 TAC GTA GAT AAT CAA AGA TTA TTA TCT ACA TTT ACT GAA TAT ATT AAG TCT AGG CCT GGA  
Y V D N Q R L L S T F T E Y I K S R P G  
2647/883 CCG GAG ACG CTC TGC GGG GCT GAG CTG GTG GAT GCT CTT CAG TTC GTG TGT GGA GAC AGG  
P E T L C G A E L V D A L Q F V C G D R  
2707/903 GGC TTT TAT TTC AAC AAG CCC ACA GGG TAT GGC TCC AGC AGT CGG AGG GCG CCT CAG ACA  
G F Y F N K P T G Y G S S S R R A P Q T  
2767/923 GGT ATC GTG GAT GAG TGC TGC TTC CCG AGC TGT GAT CTA AGG AGG CTG GAG ATG TAT TGC  
G I V D E C C F R S C D L R R L E M Y C  
2827/943 GCA CCC CTC AAG CCT GCC AAG TCA GCT GAA GCT TAG  
A P L K K P A K S A E A stop  
2617/873 2677/893 2737/913 2797/933 2857/953  
SEQ ID NO: 186  
SEQ ID NO: 187

FIG. 7

CbxA14

2587/863 TAC GTA GAT AAT CAA AGA TTA TTA TCT ACA TTT ACT GAA TAT ATT AAG TCT AGG CCT CAA  
Y V D N Q R L L S T F T E Y I K S R P Q  
2647/883 TCT AAA GTT AAA AGA CAA ATA TTT TCA GGC TAT CAA TCT GAT ATT GAT ACA CAT AAT AGA  
S K V K R Q I F S G Y Q S D I D T H N R  
2707/903 ATT AAG GAT GAA TTA TGA  
I K D E L stop  
2617/873 2677/893  
SEQ ID NO: 188  
SEQ ID NO: 189

FIG. 8

2587/863  
TAC GTA GAT AAT CAA AGA TTA TTA TCT ACA TTT ACT GAA TAT ATT AAG TCA GGC CTG AAT  
Y V D N Q R L L S T F T E Y I K S G L N  
2647/883  
TCC CCG GGT GCA GCT CAT TAT GCG CAA CAC GAT GAA GCC GTA GAC AAC AAA TTC AAC AAA  
S P G A A H Y A Q H D E A V D N K F N K  
2707/903  
GAA CAA CAA AAC GCG TTC TAT GAG ATC TTA CAT TTA CCT AAC TTA AAC GAA GAA CAA CGA  
E Q Q N A F Y E I L H L P N L N E E Q R  
2767/923  
AAC GCC TTC ATC CAA AGT TTA AAA GAT GAC CCA AGC CAA AGC GCT AAC CTT TTA GCA GAA  
N A F I Q S L K D D P S Q S A A N L L A E  
2827/943  
GCT AAA AAG CTA AAT GAT GCT CAG GCG CCG AAA GTA GAC AAC AAA TTC AAC AAA GAA CAA  
A K K L N D A Q A P K V D N K F N K E Q  
2887/963  
CAA AAC GCG TTC TAT GAG ATC TTA CAT TTA CCT AAC TTA AAC GAA GAA CAA CGA AAC GCC  
Q N A F Y E I L H L P N L N E E Q R N A  
2947/983  
TTC ATC CAA AGT TTA AAA GAT GAC CCA AGC CAA AGC GCT AAC CTT TTA GCA GAA GCT AAA  
F I Q S L K D D P S Q S A A N L L A E A K  
3007/1003  
AAG CTA AAT GAT GCT CAG GCG CCG AAA GTA GAC TAG  
K L N D A Q A P K V D  
2617/873  
2677/893  
2737/913  
2797/933  
2857/953  
2917/973  
2977/993  
3037/1013

FIG. 9

SEQ ID NO: 190  
SEQ ID NO: 191